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EDITORS' CHOICE

Predicting absolute risk of CIN3 during post-colposcopic follow-up: Results from the ASCUS-LSIL Triage Study (ALTS)

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Objective: At present, clinical management of women referred to colposcopy but found to have <CIN2 remains unclear. Using data from the ASCUS-LSIL Triage Study (ALTS) to inform clinical management, we calculated the absolute risk for developing CIN3 within 2 years of referral to an enrollment colposcopy.

Study design: Women included in the analyses: (1) were initially referred to ALTS with a community cytologic interpretation of atypical squamous cell of undetermined significance (ASCUS) or low-grade squamous intraepithelial lesions (LSIL); (2) had a colposcopic evaluation and biopsy, if indicated, resulting in a diagnosis <CIN2; and, therefore (3) were followed without treatment. Results from subsequent human papillomavirus (HPV) testing, liquid-based cytology interpretations, and a second colposcopic evaluation at least 6 months after and within 2 years of the first colposcopic evaluation were used to calculate absolute risks for CIN3.

Results: Women with HPV-negative test results were at low risk for CIN3 regardless of other test results. Among HPV-positive women, increasing absolute risks of CIN3 were observed with increasing cytology severity: 7% (normal), 11% (ASCUS and LSIL), and 45% (HSIL). The highest absolute risk for CIN3 (67%) was observed for HPV-positive women with HSIL and a colposcopic impression of high-grade/cancer on the second colposcopy.

Conclusion: In the ALTS population, after the first colposcopic diagnosis of <CIN2, clear risk stratification for CIN3 outcomes was obtained among women with a subsequent HPV-positive test. Because absolute risk for histologic CIN3 outcomes was high for women with HPV positive tests, HSIL cytology, and a high-grade impression at second colposcopy, it is worth considering whether this combination of findings might warrant immediate excisional therapy in some circumstances.

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Of all women examined through cervical cytology screening programs in the US each year, approximately 2 to 3 million women will have an abnormal or equivocal interpretation, implying increased risk for cervical cancer.[1] A successful screening program thus depends on the efficient triage of these 2 to 3 million women into differential risk categories for appropriate management and treatment.

A large proportion of CIN3 or cervical cancer comes from the work-up of low-grade or equivocal cytologic findings.[2] Overall, approximately 10% to 15% of women diagnosed with human papillomavirus (HPV)-positive atypical squamous cells (ASC) or low-grade squamous intraepithelial lesions (LSIL) will ultimately be found to have CIN3; another 10% will be found to have CIN2, albeit a less reliable diagnosis. In the ASCUS/LSIL Triage Study (ALTS), a multicenter, randomized clinical trial designed to compare management strategies for low-grade and equivocal cytologic findings, the first colposcopic examination identified about 60% to 70% of the 2-year cumulatively diagnosed CIN3, leaving the remaining lesions (either missed prevalent or incident) to be detected at a subsequent colposcopic examination or by loop electrosurgical excision procedure (LEEP) of persistent low grade HPV-related cytologic abnormalities at study exit.[3,4]

The 2001 American Society for Colposcopy and Cervical Pathology (ASCCP) management guidelines for women with a colposcopic evaluation less than CIN2 (<CIN2) have been accepted by the American College of Obstetricians and Gynecologists (ACOG) and other groups.[5,6] These guidelines recognize that for women who have <CIN2 as the colposcopic/pathologic diagnosis at their first colposcopic evaluation for LSIL or HPV-positive ASC, their risk remains elevated for more severe disease detection over the next few years. Follow-up is recommended by either repeat cytology at 6 and 12 months, or high-risk HPV testing at 12 months.[6] Any abnormal result during follow-up requires repeat colposcopic examination. In follow-up, high test sensitivity for CIN2 or CIN3 is important to identify women who should be brought back for repeat colposcopy. High positive predictive values or absolute risks for CIN2 or CIN3, however, are important for identifying the subset of women at highest risk of precancer who could be considered for immediate treatment if warranted by clinical circumstances.

In the present manuscript, we therefore examined in the ALTS population, combinations of cytologic, virologic, and colposcopic results at least 6 months after an initial colposcopic exam to determine the clinical value of these test results regarding risk of subsequent CIN2 or CIN3. Specifically, we calculated sensitivity in disease detection and absolute risks (positive predictive value) based on combinations of test results for developing CIN2 or CIN3 within 2 years of follow-up among women with histologic <CIN2 at the first colposcopic examination in ALTS.

Material and methods

Study population

The data presented here come from the prospective ASCUS/LSIL Triage Study (ALTS) sponsored by the National Cancer Institute (NCI) and conducted at 4 clinical centers from 1996 to 2000,[7] which recruited 5060 women with an LSIL (n = 1572) or ASCUS (n = 3488) cytology within the previous 6 months. Written informed consent was obtained from each subject; the study was conducted with the approval of local institutional review boards and in accordance with the NCI Institutional Review Board. The eligibility criteria, evaluation, and management schema are described in previous publications.[3,4,7] Briefly, study participants were randomized into 3 management plans: (1) immediate colposcopy; (2) HPV triage; and (3) conservative management with cytology every 6 months. In the conservative management arm, women were referred to colposcopy if they had HSIL cytology. In the HPV triage arm, women were referred when the enrollment HPV test result was positive or if they had HSIL cytology; in reality, virtually all women with HSIL were also HPV positive. During follow-up, all randomization arms were treated the same; all women were evaluated every 6 months with cytology (HPV testing was performed but blinded to the investigator until exit visit of study). Those with HSIL were referred to colposcopy. At the 24-month exit visit, all women regardless of previous trial activities were referred to colposcopy, and treatment was offered for CIN2+ or persistent low-grade cytology/histology or HPV-positive ASCUS. Treatment was by loop electrosurgical excision procedure (LEEP) or other excisional method as appropriate.

Liquid based cytology

Cytology specimens (ThinPrep, Cytyc Corporation, Marlborough, MA) were prepared as previously described.[7] Cytology interpretations were categorized according to the 1991 Bethesda System as normal, ASCUS, LSIL, or high grade squamous intraepithelial lesion (HSIL). Each ThinPrep Pap was interpreted by the clinical site pathologist and by the Pathology Quality Control (QC) Group.

HPV DNA testing

Residual PreservCyt (Cytyc Corporation) cytology aliquots were used for HPV testing via Hybrid Capture II (HC2) assay (Digene Corporation, Gaithersburg, MD), as previously described,[1,7] which included 13 oncogenic HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68).

HPV test results were thus categorized as HPV positive (for any of the oncogenic types) and HPV negative.

Colposcopic evaluation

Procedures for colposcopy followed standard clinical practice and have been previously described.[7] Colposcopic impressions were categorized as normal, low-grade, and high-grade/cancer.

Analytic population

Of the 5060 women enrolled in ALTS, 2620 women had at least 2 colposcopies 6 months apart; of these, 2031 were identified as <CIN2 at their initial colposcopy and therefore did not undergo a LEEP before their second colposcopy; this included women not biopsied because of a negative colposcopic impression. We restricted our population further to those women who also had a liquid-based cervical specimen (for cytologic interpretation and HPV testing) collected at least 6 months after their first colposcopy, resulting in a final analytic population of 1976 women. In this analytic population, the distribution of diagnoses based on the initial colposcopy and biopsy comprised 29% with no biopsy deemed necessary, 34% with a negative biopsy, and 36% with CIN1 at the initial colposcopy. As with all women in ALTS, these women with <CIN2 were observed according to ALTS protocol and followed every 6 months with cytology and blinded HPV testing; their second colposcopic evaluation was thus either triggered by HSIL cytology or done at study exit, per ALTS protocol.

Statistical analysis

Outcomes definition

Because CIN2 is the threshold for treatment, we performed the clinically relevant analysis that included CIN2 and CIN3 (CIN2+) diagnosed by clinical center pathologists during the 2-year follow-up. We used the masked, independent diagnoses of the expert Pathology QC Group to define our more stringent outcome of interest, CIN3 (includes 1 cancer).

Test definitions

We used HPV test and cytology results (as interpreted by the clinical site) from cervical specimens collected at least 6 months after the first colposcopy and before or on the day of the second colposcopy. The second colposcopic evaluation was required to be more than 6 months or 180 days after the first colposcopy.

We evaluated absolute risks over the 2-year ALTS follow-up for CIN2+ (n = 194) and CIN3 outcomes (n = 127) based on cytologic, virologic, and colposcopic results obtained at least 6 months subsequent to their first colposcopic evaluation. Absolute risks (ie, positive predictive values) were defined as the percentage of women diagnosed with the disease endpoint given a specific positive test result or combination of results; respective 95% confidence intervals were also calculated for each independent test modality and for each test combination. In addition to the overall analyses, we also conducted analyses stratified by referral status (LSIL vs ASCUS) and by age (<30 and ≥30 years). Finally, we also calculated the sensitivity (percentage) of detecting CIN2+ and CIN3 outcomes, for each test combination. Individuals with missing values were considered in separate categories and the numbers varied for each test combination assessed. All analyses were conducted using SAS version 8.2 (SAS Institute, Inc, Cary, NC).

Results

Among women with an initial colposcopy/biopsy of <CIN2 that thus did not warrant treatment, a single subsequent HPV test result was positive in 48% of women and demonstrated a high sensitivity of 84% for identifying CIN3 detected within 2 years. Despite the high sensitivity of a positive HPV result, the absolute risk (which equals positive predictive value) for developing CIN3 within 2 years in HPV-positive women was only 12% (Table I). HPV-negative women were highly unlikely to have CIN3 diagnosed (2%).

Compared with HPV testing, the sensitivity of cytology at various test thresholds was significantly ($P = .015$) lower for identifying CIN3: ≥ASCUS (72%), ≥LSIL (43%), and HSIL (23%). The absolute risk for CIN3 was low for a cytology interpretation of normal (3.1%), ASCUS (7.9%), or LSIL (9.2%) but substantially greater for an interpretation of HSIL (42%) (Table I). Similar results were observed for CIN2+ outcomes (Table II).

Adding cytology to HPV testing did not increase sensitivity for CIN3 compared with HPV testing alone, but the combination of tests did further stratify risk, resulting in the following absolute risks for CIN3 among HPV-positive women: 7% for normal cytology, 11% for both ASCUS and LSIL, and 45% for HSIL (Table I). Notably, 91% of women with LSIL or HSIL cytology interpretations were HPV-positive, explaining the relatively small differences in absolute risk for these cytology interpretations with or without considering HPV test results. The low absolute risk for normal cytology (3.1%) was even lower among HPV-negative women (1.2%).

In conjunction with HPV and cytology results, the colposcopic impression from the second examination offered the finest level of absolute risk discrimination in our data. For example, among women with HPV-positive test results, for each severity of cytology interpretation, absolute risks tended to increase by severity of

Table I Absolute risks for post-colposcopic 2- and 3-stage strategies for CIN3 outcome (as defined by the pathology review panel) in ASCUS and LSIL cytology referrals, using second colposcopic impression

ThinPrep Pap		Hybrid Capture 2					
		Negative			Positive		
# CIN3/total	**Absolute Risk (%)**	**# CIN3/total 19/962**		**Absolute Risk (%) 2.0**	**# CIN3/total 103/874**		**Absolute Risk (%) 11.8**
Normal		**9/726**		**1.2**	**25/344**		**7.3**
		Colposcopy	# CIN3/total	Absolute Risk (%)	Colposcopy	# CIN3/total	Absolute Risk (%)
36/1157	**3.1**	Normal	1/401	0.2	Normal	3/135	2.2
		Low grade	8/308	2.6	Low grade	18/195	9.2
		High grade/CA	0/13	0	High grade/CA	3/9	33.3
ASCUS		**10/199**		**5.0**	**26/240**		**10.8**
		Colposcopy	# CIN3/total	Absolute Risk (%)	Colposcopy	# CIN3/total	Absolute Risk (%)
37/466	**7.9**	Normal	0/100	0	Normal	2/69	2.9
		Low grade	9/94	9.6	Low grade	20/158	12.7
		High grade/CA	1/4	*	High grade/CA	4/11	36.4
LSIL		**0/25**		—	**24/225**		**10.7**
		Colposcopy	# CIN3/total	Absolute Risk (%)	Colposcopy	# CIN3/total	Absolute Risk (%)
25/273	**9.2**	Normal	0/12	0	Normal	1/55	1.8
		Low grade	0/13	0	Low grade	19/149	12.7
		High grade/CA	—	—	High grade/CA	4/19	21.0
HSIL		**0/4**		—	**28/62**		**45.2**
		Colposcopy	# CIN3/total	Absolute Risk (%)	Colposcopy	# CIN3/total	Absolute Risk (%)
29/69	**42.0**	Normal	0/1	0	Normal	1/1	*
		Low grade	0/3	0	Low grade	15/43	34.9
		High grade/CA	—	—	High grade/CA	12/18	66.7

Cytology predicts CIN 3 absolute risk in second column (bolding). Absolute risks for CIN3 by HPV negative and HPV positive results are presented in the top row (bolding). In the columns below this, the risk by HPV result is further stratified according to cytology result. Finally, the risk groups defined by HPV and cytology results are further stratified by colposcopy impression. For example, HPV + absolute risk of CIN 3 overall is 11.8% in last column. HPV+ is then stratified below by cytology result values of 7.3 (nl); 10.8 (ASCUS); 10.7 (LSIL); and 45.2 (HSIL). Finally, HPV+/cytology result are stratified by colposcopy impression (ie, HPV+/HSIL with high grade colposcopy has a CIN3+ absolute risk of 66.7%).

* Denominator <5.

colposcopic impression. At the extreme high end of positive predictive value (PPV), among women with HPV-positive HSIL, the absolute risk of CIN3 was 35% for those with low-grade colposcopic impressions and 67% for high-grade colposcopic impressions (Table I).

Similar patterns to those observed for CIN3 outcome were also observed for the CIN2+ outcomes (Table II). As expected, absolute risks were in general higher because the disease endpoint was less stringent. Consistent with what we observed for CIN3 outcomes, the lowest absolute risk was observed for the combination of normal cytology interpretation, negative HPV test result, and normal colposcopic impression (0.2%); in contrast, the highest absolute risk for CIN2+ was observed for women with an HPV-positive HSIL and a high-grade/cancer colposcopic impression (78%). As with CIN3 outcomes, the elevated risks of SIL cytology and abnormal colposcopic impression were seen most clearly among women with positive HPV test results.

Finally, without consideration of post-colposcopic cytology, we calculated absolute risks for HPV positive women using colposcopic impression from the second colposcopy; there were 260 normal, 545 low-grade, and 57 high-grade impressions predicting absolute risks for CIN3 of 2.7%, 13.2%, and 40.4%, respectively (Table III). Interestingly, most CIN3 cases were associated with low-grade colposcopic impressions (69.6%), not high-grade (22.3%). The results for CIN2+ were entirely consistent (Table III).

Comment

To examine the possible value of different diagnostic tests in the post-colposcopic management of women

Table II Absolute risks for post-colposcopic 2- and 3-stage strategies for CIN2+ outcome (as defined by the clinical centers) in ASCUS and LSIL cytology referrals, using second colposcopic impression

ThinPrep Pap		Hybrid Capture 2					
		Negative			Positive		
# CIN2+/total	**Absolute Risk (%)**	**# CIN2+/total 23/962**		**Absolute Risk (%) 2.4**	**# CIN2+/total 168/874**		**Absolute Risk (%) 19.2**
Normal		**13/726**		**1.8**	**38/344**		**11.0**
		Colposcopy	# CIN2+/total	Absolute Risk (%)	Colposcopy	# CIN2+/total	Absolute Risk (%)
53/1157	4.6	Normal	1/401	0.2	Normal	5/135	3.7
		Low grade	11/308	3.6	Low grade	29/195	14.9
		High grade/CA	1/13	7.7	High grade/CA	3/9	33.3
ASCUS		**7/199**		**3.5**	**46/240**		**19.2**
		Colposcopy	# CIN2+/total	Absolute Risk (%)	Colposcopy	# CIN2+/total	Absolute Risk (%)
54/466	11.6	Normal	0/100	0	Normal	6/69	8.7
		Low grade	6/94	6.4	Low grade	34/158	21.5
		High grade/CA	1/4	25.0	High grade/CA	6/11	54.5
LSIL		**0/25**		—	**43/225**		**19.1**
		Colposcopy	# CIN2+/total	Absolute Risk (%)	Colposcopy	# CIN2+/total	Absolute Risk (%)
44/273	16.1	Normal	0/12	0	Normal	3/55	5.5
		Low grade	0/13	0	Low grade	34/149	22.8
		High grade/CA	—	—	High grade/CA	6/19	31.6
HSIL		**0/4**		—	**41/62**		**66.1**
		Colposcopy	# CIN2+/total	Absolute Risk (%)	Colposcopy	# CIN2+/total	Absolute Risk (%)
43/69	62.3	Normal	0/1	0	Normal	1/1	*
		Low grade	0/3	0	Low grade	26/43	60.5
		High grade/CA	—	—	High grade/CA	14/18	77.8

Absolute risk of CIN 2+ for each cytologic diagnosis is shown in the second column (bolding). Absolute risks for CIN2+ by HPV negative and HPV positive results are presented in the top row (bolding). In the columns below this, the risk by HPV result is further stratified according to cytology result. Finally, the risk groups defined by HPV and cytology results are further stratified by colposcopy impression. For example, the absolute risk of CIN 2+ for HPV + result overall is shown in the last column or 19.2%. The HPV + absolute risk for CIN 2+ is then stratified for each cytology result in the last column 11% (nl); 19.2% (ASCUS); 19.1 (LSIL); and 66.1 (HSIL). The final stratification is for colposcopic impression where HPV+/HSIL/high grade colposcopy patient has a 77.8% absolute risk of CIN 2+.

* Denominator <5.

examined initially for LSIL or HPV-positive ASCUS, we followed 1976 women enrolled in ALTS whose first colposcopic examination was less than CIN2 (ie, no treatment). For these women, follow-up cytology and HPV testing results at least 6 months after their initial colposcopy were evaluated in addition to their colposcopic impression from a second colposcopic examination, which occurred at least 6 months after their first colposcopic examination. The median time interval between the first and second colposcopy in this population was 24 months. We evaluated the test sensitivity and positive predictive value for both CIN3 and CIN2+ outcomes, as CIN2+ represents the threshold for treatment per current US practice.

We were able to estimate the absolute risk of subsequent CIN2+ or CIN3 for women based on HPV test results, cytology interpretations, and colposcopic impressions, either individually or in combination. In our data, about half of the women had a positive follow-up HPV test for carcinogenic types (as a group) that provided sensitivity of 84% for subsequent CIN3, but yielded a low absolute risk (12%) for CIN3. In other words, many HPV-positive women did not develop CIN3 within our study and probably never would. Further, because most women with CIN3 were also HPV-positive, adding cytology concomitant with HPV testing did not contribute towards increased sensitivity for CIN3 or CIN2+ endpoints. Nevertheless, the combination did further stratify women according to disease risk, as did the addition of a second colposcopic impression. On the other hand, an HPV-negative test result was associated with only a small residual risk for CIN3 of 2%.

Table III Absolute risks for CIN3 and CIN2+ diagnosis in HPV positive ASCUS/LSIL women at second colposcopy by colposcopic impression

	HPV positive women (n = 874)		
Second colposcopic impression (n = 862)	# CIN3	% of all CIN3	Absolute risk of CIN3 by colposcopic impression
Normal (n = 260)	7	6.8%	2.7%
Low grade (n = 545)	72	69.6%	13.2%
High grade (n = 57)	23	22.3%	40.4%
	HPV positive women (n = 874)		
Second colposcopic impression (n = 862)	# CIN2+	% of all CIN2+	Absolute risk of CIN2+ by colposcopic impression
Normal (n = 260)	15	8.9%	5.8%
Low grade (n = 545)	123	73.2%	22.6%
High grade (n = 57)	29	17.3%	50.8%

Absolute risk of CIN 3 during follow-up after ASCUS/LSIL Pap and colposcopic examination $\leq$CIN 2 is predicted with HC2 and colposcopic impression.

Given an HPV positive test result, the additional contribution of cytology to stratifying absolute risk was substantial only when cytology was HSIL. Women with HPV positive test results and HSIL had a 45% absolute risk for CIN3 and a 66% risk of at least CIN2. Immediate treatment might be a consideration for this small subset of women with positive HPV, cytologic HSIL, and high-grade colposcopic impression if there is concern regarding loss to follow-up.

Our data further suggest that if we were to forego cytology entirely and combine HPV testing with colposcopic impression, the combination of HPV-positive test result and a high-grade colposcopic impression would yield a slightly lower 40% absolute risk for CIN3 and only a 51% absolute risk for CIN2+ (Table III). Among women with subsequently detected CIN3 at the second colposcopy, 7 had a negative colposcopic impression, 72 a low-grade, and 23 a high-grade impression. This suggests the lack of sensitivity of colposcopic procedures and at a minimum confirms the recommendation that at least 1 or 2 biopsies should be performed for all women with any lesion, not just those with high-grade impressions.

Finally, the identification of a few CIN3 outcomes with HPV-negative test results points out that even the most sensitive test cannot provide perfect reassurance against risk of cancer. Notably, 19 women had a single HPV-negative test result before or concurrent with their second colposcopic evaluation leading to diagnosis of CIN3; of these, 9 were also cytologically normal and 10 were interpreted as ASCUS. A review of complete trial visit histories for these women identified previous HPV-positive test results, suggesting the single negative HPV test result was falsely negative.

These results extend our previous report of disease risk stratification at first colposcopy where we demonstrate that a concurrent HPV-positive test result, HSIL cytology, and high-grade visual inspection of the cervix can pinpoint a small group of women at extremely high risk of cervical precancer.[8] Although concurrent test results were available for risk evaluation due to the research infrastructure provided by ALTS, such a concurrent multitest strategy would be inefficient for triage or screening.

Although ALTS was not specifically designed to investigate post-colposcopic management strategies, strengths of the present analysis include the prospective nature and high retention rates of the trial. Nearly all women had colposcopy at exit at which point the treatment threshold was lowered to include LEEP of persistent low-grade lesions in addition to CIN2+. While this study design provided virtually complete ascertainment of disease, it may also be a limitation in that many of the CIN2+ lesions found at exit were small. At present, the benefit of detecting such lesions is not clear, particularly for small CIN2.

In ALTS, lowering the threshold for LEEP at exit to include persistent low-grade lesions (in the absence of biopsy detected CIN2+) did yield some cases of CIN3, indicating residual risk for CIN3 even after a second colposcopic result of <CIN2. We do not yet know how long women who are <CIN2 but persistently HPV positive should be followed without treatment outside the context of a clinical trial. Gage has reviewed the ALTS investigators' colposcopic training and number of biopsies performed, which demonstrated some informative results. Taking more biopsies substantially increases the detection of CIN3; therefore, multiple biopsies at the time of colposcopy might be preferable to the alternative of 1 biopsy of the most concerning lesion.[9]

In conclusion, our results show that because colposcopically directed biopsies are not completely sensitive for the detection of CIN2+, women identified as <CIN2 at initial colposcopy remain at risk for subsequent CIN2+. Follow-up HPV testing is significantly

more sensitive than cytology ($P = .015$) for detecting missed prevalent cases, but refers almost half of women for repeat colposcopy. Although cytology does not improve sensitivity for disease detection beyond a subsequent HPV test and colposcopy, the highest absolute risk and thus positive predictive value for disease was observed with the combination of a high-grade cytology interpretation and high-grade colposcopic impression among HPV-positive women. The ancillary use of cytology might thus be justified if immediate treatment for the highest risk women is clinically warranted because of concern of loss-to-follow up. Additional discourse regarding what threshold of absolute risk would warrant excisional therapy ("See and Treat") is thus needed at the present time.[10-13] It is plausible that management strategies could be tailored towards a woman's characteristics (eg, age, desire for fertility, follow-up compliance), according to different combinations of test results. Competing risks of undertreatment, which potentially results in loss to follow-up and subsequent cancer, must be balanced with the risks of overtreatment, which, although rare, may include premature births, premature rupture of membranes, and low-birth-weight infants.[14-16] The threshold of absolute risk which would be appropriate for immediate excisional therapy can thus be individualized to patient needs and preferences. This report will be of value to those who manage or treat women with low-grade cytologic findings.

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